

CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY



EFMC

International Symposium
on Medicinal Chemistry

Lisbon, Portugal September 7-11, 2014

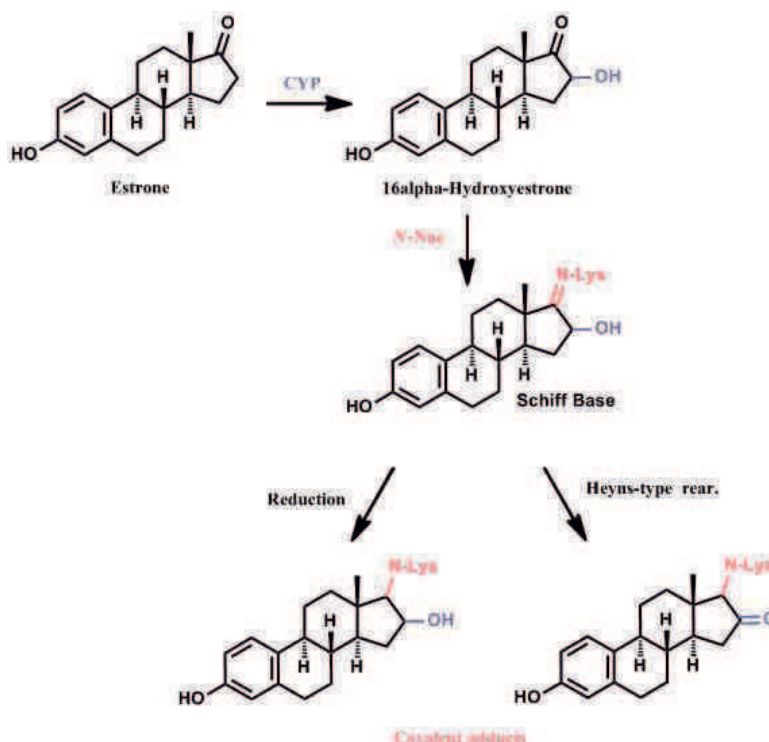
A Journal of



ChemPubSoc
Europe

**BOOK OF
ABSTRACTS**

WILEY-VCH



Acknowledgements:

This work was supported by FCT, Portugal, through grants PEST-OE/QUI/UI0100/2013 and RECI/QEQ-MED/0330/2012. Thanks are also due to the Portuguese NMR Network (IST-UL Center).

References:

- [1] Cutolo et al. *Autoimmun. Rev.* **2012**, 11, A460–A464.
- [2] Iverson et al. *Chem. Res. Toxicol.* **1996**, 9, 492–499.
- [3] Cerami et al. *Proc. Natl. Acad. Sci. USA* **1982**, 79, 3320–3324.
- [4] Fishman et al. *Biochemistry* **1985**, 24, 8017–8021.
- [5] Cerami et al. *Eur. J. Biochem.* **1984**, 140, 593–598.

Y015 | Chalcones as Promising Small-Molecule Inhibitors of p53–MDM2 Interaction

Pedro Brandão,⁽¹⁾ Sylvie Carvalho,⁽¹⁾ Daniela Pereira,⁽¹⁾ Joana Soares,⁽²⁾ Sara Cravo,^(1,3) Lucília Saraiva,⁽²⁾ Madalena Pinto,^(1,3) Honorina Cidade^(1,3)

1) Centro de Química Medicinal da Universidade do Porto (CEQUIMED-UP) e Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal

2) REQUIMTE, Laboratório de Microbiologia, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal

3) Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR/CIMAR), Universidade do Porto, Rua dos Bragas, 289, 4050-123 Porto, Portugal

The p53 tumor suppressor protein is one of the major regulators of cell proliferation and death. Therefore, p53 is considered a key protein in cancer development. The activity and stability of p53 are regulated by the endogenous negative regulator, MDM2. Hence the discovery of inhibitors of p53–MDM2 interaction is considered a promising strategy for cancer treatment.^[1] Chalcones represent an outstanding class of plant secondary metabolites, which have long been recognized for their pharmacological properties, being the antitumor activity one of the most extensively studied. Previous studies from our research group have shown potent growth inhibitory effects of several prenylchalcones against distinct human tumor cell lines.^[2] Taking this in consideration, and with the objective of obtaining chalcones with potential antitumor activity by interfering with the p53–MDM2 interaction, several prenylchalcones were synthesized using the chalcone as building block with prenyl bromide in presence of tetrabutylammonium hydroxide at room temperature. Structure elucidation was performed by NMR techniques (¹H NMR, ¹³C NMR, HSQC and HMBC). The effect of the synthesized chalcones on the p53–MDM2 interaction was evaluated using a yeast-based assay, consisting of *Saccharomyces cerevisiae* cells co-expressing human p53 and MDM2, as described previously.^[3]

Acknowledgements:

This work was funded by FCT – Fundação para a Ciência e a Tecnologia under the project CEQUIMED – Pest-OE/SAU/UI4040/2014 and REQUIMTE (Pest-C/EQB/LA0006/2013) FEDER funds and COMPETE program under the projects FCOMP-01-0124-FEDER-011057 and FCOMP-01-0124-FEDER-015752.

References:

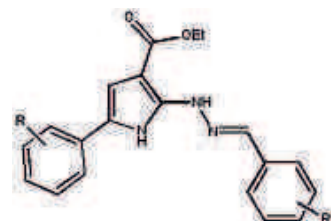
- [1] *Targeting the MDM2-p53 protein–protein interaction for new cancer therapeutics*. S. Wang, Y. Zhao, D. Bernard, A. Aguilar, S. Kumar, *Top Med. Chem.* **2012**, *8*, 57–80.
- [2] *Synthesis of a natural chalcone and its prenylated analogues–evaluation of tumor cell growth inhibitory activity and effects on cell cycle and apoptosis*. M.P. Neves, R.T. Lima, K. Choosang, P. Pakkong, M.S.J. Nascimento, M.H. Vasconcelos, M. Pinto, A.M.S. Silva, H. Cidade, *Chem. Biodivers.* **2012**, *9*, 1133–1143.
- [3] *Discovery of a new small-molecule inhibitor of p53-MDM2 interaction using a yeast-based approach*. M. Leão, C. Pereira, A. Bisio, Y. Ciribilli, A.M. Paiva, N. Machado, A. Palmeira, M.X. Fernandes, E. Sousa, M. Pinto, A. Inga, L. Saraiva, *Biochem. Pharmacol.* **2013**, *85*(9), 1234–1245.

Y016 | Design, Synthesis and Evaluation of New 2-(Arylidenehydrazino)pyrrole Derivatives as Potential Antitumor Agents

Cenzo Congiu, Valentina Onnis, Alessandro Deplano, Monica Demurtas, Gianfranco Balboni

Department of Life and Environmental Sciences, Unit of Medicinal, Pharmacological and Nutraceutical Sciences, University of Cagliari, Via Ospedale 72, Cagliari 09124, Italy

Hydrazone derivatives constitute a class of compounds intensively investigated as target for drug development. Experimental and preclinical models demonstrated that a number of these compounds elicited outstanding anticancer activity through a range of biological activities implicated with the development and maintenance of tumor cells. Recently, we have reported the synthesis and in vitro antitumor activity of various heterocyclic acylhydrazone derivatives. Several of tested compounds exhibited in vitro excellent antiproliferative effect against the NCI full panel cell lines, showing low micromolar to nanomolar GI₅₀ inhibitory values, and no sign of acute toxicity in athymic nude mice.^[1] In a previous study, we reported some arylidenehydrazinopyrimidines endowed with inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{−5} M to 10^{−7} M concentrations.^[2] Within the context of our research program, we designed new 2-(arylidenehydrazino)pyrrole derivatives in order to be evaluated as potential antitumor agents (see Figure). The synthesis of a series of these compounds, results of the in vitro antiproliferative activity, and initial SAR study are discussed.



References:

- [1] (a) V. Onnis, M. T. Cocco, R. Fadda, C. Congiu, *Bioorg. Med. Chem.* **2009**, *17*, 6158; (b) C. Congiu, V. Onnis, *Bioorg. Med. Chem.* **2013**, *21*, 6592.
- [2] M. T. Cocco, C. Congiu, V. Lilliu, V. Onnis, *Bioorg. Med. Chem.* **2006**, *14*, 366.

Y017 | Antiproliferative Activity of N-Acylhydrazone Derivatives Designed as Tubulin Polymerization Inhibitors

Daniel do Amaral,⁽¹⁾ Bruno Cavalcanti,⁽²⁾ Daniel Bezerra,⁽²⁾ Paulo Michel Ferreira,⁽³⁾ Camila Machado,⁽³⁾ Roger Chammas,⁽⁴⁾ Claudia Pessoa,⁽²⁾ Eliezer Barreiro,⁽¹⁾ Lídia Lima⁽¹⁾

1) Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos (INCT-INOVAR; www.inct-inovar.ccs.ufrj.br), LASSBio®, Universidade Federal do Rio de Janeiro. PBOX 68006, CEP 21941-971, Rio de Janeiro-RJ, Brasil

2) Departamento de Fisiologia e Farmacologia, Faculdade de Medicina, 60.430-270, Fortaleza, CE, Brasil

3) Departamento de Ciências Biológicas, Campus Senador Helvídio Nunes de Barros, Universidade Federal do Piauí, 64.607-670, Picos, PI, Brasil

4) Faculdade de Medicina, Departamento de Radiologia, Universidade de São Paulo, 01246-903, São Paulo, SP, Brasil

Cancer is the second cause of death in USA and this term represents a group of diseases characterized by an untypical growth of cells in different tissues.^[1] The treatment is based on use of one or more drugs able to interfere at cell division cycle.^[2] Among these chemotherapies, those who interrupt the microtubules dynamic, like vincristine and paclitaxel, were demonstrated to have high efficacy in treatment of several tumors. Therefore, compounds able to inhibit tubulin polymerization are considered a promise cytotoxic agent with potential antitumor activity.^[3,4]

Based on combretastatin A4 (CA-4), a natural stilbene isolated from *Combretum caffrum*, that binds to the colchicine domain on β -tubulin and acts as anti-microtubule agent, a congener series of N-acylhydrazone derivatives were designed as CA4 analogues. Herein, we describe the docking studies, the synthesis and the antiproliferative activity against different human tumor cell lines (HL-60, SF295, MDA-MB435, HCT-8, PC3M, OVCAR-8 and NCI-H358M) of these N-acylhydrazone derivatives. The main structural requirements essential to molecular recognition process by the colchicine binding site of β -tubulin were recognized and several compounds with